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LIVING GRAFTS OF ENDOCRINE GLANDS*

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I

AT present perhaps no field in medicine is the focus of greater interest than that known as endocrinology. General medicine and general surgery concern themselves actively with the study and treatment of disorders of the thyroid, the parathyroids, the islands of Langerhans, the hypophysis, and the more recently investigated adrenals. The subdivisions of clinical medicine are all touched to some extent by the ramifications of the general subject of endocrinology. Just now workers in obstetrics and gynecology are so successful in describing new hormones of conflicting or coöperating properties that one not closely engaged in these particular branches is more than a little bewildered. To keep pace with the terminology alone is no simple matter for an outsider. We find the brain surgeon, the urologist, and the gynecologist each depicting a nearly identical clinical state of general constitutional disturbance with changes of sexual characteristics and metabolism, but the first attributes this to tumor of the hypophysis, the second to tumor of the adrenal, and the third to tumor of the ovary. Not only clinical medicine, but the allied sciences are busily engaged. Pathology has furnished us with descriptions of the lesions of the organs concerned, and physiology has revealed much of their functions—the foundation on which rest our clinical conceptions. By no means least remarkable has been the contribution of biological chemistry, for surely epinephrin, thyroxin, insulin, cortin, and parathormone rank among the major achievements of recent times in the medical sciences. We are even told that characters, personality, and various other less tangible qualities depend upon the glands of internal secretion. In fact, we have been told so much, and much of it so evidently based largely on imaginative theory, not to say romance, that the more conservative are inclined to view the

whole subject of endocrinology with a certain judicious reserve. But making all allowance for overenthusiasm in a rapidly expanding and rather "miraculous" field, the solid and indisputable advance has been nothing less than monumental. When one recalls that until the work of Claude Bernard¹ only faint glimmerings of the real nature of internal secretion existed, and contrasts this with the practical results now attained in such common disorders as goiter and diabetes, there emerges a sharp realization of the important progress thus far attained. For the purpose of this paper, it may be well to direct further attention to the nature of this progress.

SOME BASIC GENERAL KNOWLEDGE

Certain general ideas are easily recognizable as basic in all the firmly established knowledge of the glands of internal secretion. These may be briefly stated as follows, and need no elaboration. First, the products of these glands, the hormones or internal secretions, are essential to life, even though their actual quantity may be relatively very small. Second, an excess in amount or perversion in quality of the secretion causes marked changes in general bodily function; these changes are characteristic for the particular gland concerned, as a rule; and are in some cases measurable by definite chemical and physical tests. Third, a deficiency of secretion, not so profound as to be promptly fatal, also causes marked and characteristic changes in bodily function which are more or less the antithesis of those that go with excessive secretion. From the viewpoint of clinical medicine, these basic ideas find their application in the two great fields of diagnosis and treatment. A most interesting historical survey might be made of the way in which clinical states, well recognized and described before endocrinology existed even as a name, have since come to be understood as manifestations of disorders of the glands of internal secretion. One thinks of Graves' disease, of Addison's disease, of acromegaly, of diabetes, of Paget's disease of the bones—and in passing salutes the powers of observation and synthesis of the great clinicians who drew from obscurity a sharp picture of a disease entity. But it is particularly with problems of treatment that we wish to concern ourselves in this paper, and we proceed to consider the general lines along which these problems have been attacked.

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TWO GROUPS OF ENDOCRINE GLAND DISORDERS

It is clear from what has just been said—a matter of common general knowledge—that disorders of the endocrine glands fall readily into two groups, the disorders of excess and those of deficiency. Of the first group the outstanding familiar example is toxic goiter; of the second, diabetes. Likewise the principles of treatment obviously are divisible into two corresponding groups, if one leaves out of consideration for this discussion the palliative, indirect, and supportive treatments that do not directly attack the root of the trouble. For the disorders of excessive secretion the direct treatment is aimed at the destruction of enough of the gland concerned to bring back its production of secretion within normal limits, but with care to preserve sufficient tissue for proper function. The usual method of attaining this purpose is surgical removal of the offending structure, although other destructive agencies, such as radiation, have been used for the same end. The story of the operative treatment of goiter illustrates well how the surgery of endocrine excess has evolved, and it has been told in unsurpassable manner by Halsted.² The lessons learned on this particular gland of internal secretion are being widely applied to similar problems in other glands. The hypophysis has its story, too, and the stories of the parathyroid, of the adrenal, and of the gonads considered as glands of internal secretion, are being busily written now. There will undoubtedly be much to learn. In some cases improvements of approach and technique, in others of preparation and extent of removal. It may be said safely, however, that the principle of treatment for disorders of excessive glandular activity is established.

A PRINCIPLE IN USE IN INTERNAL SECRETION DEFICIENCIES

There has been developed also a principle for dealing with deficiency of internal secretion. That principle is the discovery, through chemical investigation, of the active principle lacking, and its administration to make good the lack. Here we enter a very recent and very dramatic field of development. Insulin, parathormone, and cortin are fresh in the minds of everyone as great discoveries almost of yesterday, and constant work is being done along similar lines with other important organs of internal secretion. These advances have prolonged lives and relieved suffering in a way that was quite impossible ten years ago, and the field is still a large and fertile one for further cultivation. Great as these achievements are, however, and richly as they deserve the gratitude and appreciation of all mankind, they yet fall short of the ideal. For it is obvious that any method requiring the constant administration from without the body of substances essential to its welfare, that are normally produced within it, lacks much of being a satisfactory arrangement. The ideal, the goal clearly before us is to restore to the body the power to form its own necessary internal secretion. This brings us, after perhaps too long an approach, to the direct purpose of this paper.

We have undertaken to graft into animals living endocrine tissues in the hope of providing a better method of treatment of the deficiency disorders of the glands of internal secretion, and this paper is a preliminary report of that work.

LIVING GRAFTS OF ENDOCRINE GLANDS

The problem has not been attacked without some understanding of its difficulties or some knowledge of the many previous attempts that have been made in the same direction. It has been generally accepted that it is nearly impossible to succeed in grafting living tissue from one animal to another. Perhaps the most frequent and most ancient effort in this general field has concerned skin grafting. In this particular form of cross grafting, as elsewhere, it is the consensus of opinion that the grafts do not survive even when special measures, such as matching the blood of donor and recipient are observed. Holman³ has reported on this. A few optimists, however, like J. Staige Davis, with his great experience of plastic surgery, believe that in rare instances such grafts do survive. We shall not discuss the many efforts that have been made to cross graft living bone, fascia, nerve, etc., nor the almost uniform failure that has been reported. We do wish, however, to deal briefly with some of the problems and difficulties that are involved. It is clear that certain conditions are essential to success of the graft. The most important of those known are the securing of a prompt and adequate blood supply to the graft, the avoidance of strangulation by surrounding tissues, especially scar, and the provision of chemical affinity, in its broadest sense, between the graft and the host tissues. There may be many other factors of which we are entirely ignorant.

CROSS GRAFTING

The problem of cross grafting endocrine tissue is in one respect much simpler than grafting bone, tendon, or nerve. In the case of the endocrine glands the essential element is the individual cell with its peculiar secretory properties, whereas in the other instances not only the living cell but features of structural arrangement and architecture are important. Attempts at transplantation of glands of internal secretion are not new. Halsted,⁴ in particular, made extensive experiments in this field. He was interested particularly in the thyroid and parathyroid, and reported that he was never able to succeed in transplanting parathyroid tissue from one animal into another. In several instances he proved that he had transplanted functioning parathyroids to new sites in the same animal, but only after he had created a deficiency of parathyroid by previous removal of some of the glands. It was upon this work that he suggested his well known "law of deficiency," namely, that for the graft of an endocrine gland to be successful, the animal must be in physiologic need of the gland because of a created deficiency. It has been assumed rather generally that Halsted definitely proved this thesis and it is accepted as established. As a matter of fact, it was merely

a suggestion made by him with the specific statement that further work would be required to prove it. We shall make reference to this matter again later. This situation was one of the impelling influences that led to our own studies, for the demonstration by Halsted of at least a measure of success in autotransplantation of parathyroids encouraged hope, and we were impressed by two further considerations. One of these was the importance of the fact noted above that survival of even fragments of glands would be adequate and the other was the help that might be gained from the teachings and experiences of those who have cultured tissues for long periods of time *in vitro*. As we interpreted these teachings, it seemed that the essential conditions were as follows: the tissue must be surrounded by a particularly suitable nutrient medium; it must be maintained in such small fragments that most of the cells can come into direct and intimate contact with this medium, for here there is no circulation; and finally, the fragments must be free from pressure and protected from infection.

(To be concluded)

PROSTATIC OBSTRUCTION—DEVELOPMENT OF ITS SURGICAL TREATMENT*

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I

BECAUSE the distressing symptoms of prostatism so frequently interfere with the pursuit of happiness in later life the physician has always entertained a keen personal as well as professional interest in the disease. The subject seems particularly fitting for review this year, as it is the centenary of the first efforts by Guthrie to correct prostatic obstruction through the urethra, and from all indications this year will witness the general abandonment of prostatectomy, either perineal or suprapubic, for some method of transurethral treatment. As now practiced the transurethral procedure gives relief of symptoms without incurring the risk of major surgery, avoids prolonged hospitalization, and is not followed by distressing evidences of dysfunction such as incontinence, persisting urinary fistulas and other unfortunate sequels so frequently seen after prostatectomy.

EARLY HISTORICAL REFERENCES

In tracing the development of the surgical treatment of prostatism one must turn back to the seventeenth century when, as those who have perused Pepy's Diary will recall, "cutting for stone" was an accepted surgical procedure. During the next century adventurous surgeons occasionally attempted the same operation for the relief of urinary obstruction, even when the metallic sound did not elicit the click characteristic

of the presence of a calculus. In 1809 Blizard¹⁴ was able to report a series of cases of urinary obstruction from prostatic hypertrophy which were relieved by this operation. Such leaders in surgery as Fergusson considered it the accepted method of treatment when the catheter had failed.

Home, in 1811, published an essay entitled "Practical Observations on the Treatment of the Diseases of the Prostate Gland." He described hypertrophy of the posterior commissure so accurately that Randall has recently suggested that the term "Home's lobe" be applied to this pathologic entity in place of "median lobe," because the latter term tends to confound the changes brought about by hyperplasia with those produced by atrophy and commonly referred to as median bar.

MEDIAN BAR OBSTRUCTION

Median bar. This variety of urinary obstruction was first called "median bar formation" by Guthrie in 1834, and although other terms have been suggested, such as "contracture of the vesical neck," "sclerosis of the internal sphincter," and "fibrosis of the vesical orifice," there seems to be no good reason to depart from the original terminology if we keep its pathology clear in our minds. Randall, who has carefully studied the pathologic changes of the prostate gland, described the condition as: "Fibrosis which by its inevitable shrinkage stenosis of the bladder orifice produces residual urine and gives all the symptoms of prostatism. All evidence points to this fibrosis being the result of long-standing prostatic infection, and there is no evidence to gainsay such as the probable etiologic factor." Because the symptoms of such obstruction are frequently identical with those produced by hyperplasia, the term "prostatisme sans prostate" had been applied.

The median bar, of course, offers the best type of case to treat by some form of incision carried out through the urethra, and until recently many eminent urologists regarded it as the sole variety of urethral obstruction for which correction by the transurethral route was suitable. Guthrie was the first to make such an attempt, and in a paper read before the Royal College of Surgeons in 1834, he described division of the obstructing bar at the neck of the bladder by incising it with a knife-blade hidden in the eye of a catheter, in much the same way that internal urethrotomy was performed some years later. He believed that the bar was the result of tautening of the mucous membrane between the hypertrophic lateral lobes. A procedure for correcting such obstruction has been brought to full perfection in recent years by Collings of New York, who employs a high frequency cutting current in conjunction with a small, hooked platinum knife, and a more accurate procedure is hard to imagine. In the absence of hyperplasia only small amounts of tissue require excision.

Mercier, in 1837, devised two instruments called at the time by Gouley "prostatotome" and "prostatactome" for transurethral correction of prostatic obstruction. The first instrument accomplished

* From the Section on Urology, The Mayo Clinic, Rochester, Minnesota.

* Stanley P. Black Memorial Lecture, Pasadena, California, January 16, 1933.